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NEWS EXPRESS OCTOBER 29 CURRENT WINDOWS VERSION IS V7.01A, CURRENT  
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FILE 'MEDLINE' ENTERED AT 18:25:43 ON 29 NOV 2004

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=> s (selective serotonin reuptake inhibitor) or ssri  
L1 8143 (SELECTIVE SEROTONIN REUPTAKE INHIBITOR) OR SSRI

=> s l1 and CYP2D6  
L2 181 L1 AND CYP2D6

=> s l2 and pharmacophore  
L3 0 L2 AND PHARMACOPHORE

=> s 12 and qsar  
L4 0 L2 AND QSAR

=> s 12 and py<2000  
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=> s 14 and py<1999  
L5 0 L4 AND PY<1999

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L6 90 L2 AND PY<1999

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=> s 17 and review/dt  
L8 25 L7 AND REVIEW/DT

=> d 1-25 bib ab

L8 ANSWER 1 OF 25 MEDLINE on STN  
AN 1999246031 MEDLINE  
DN PubMed ID: 10231000  
TI Behavioral disturbances of dementia.  
AU Pollock B G; Mulsant B H  
CS Department of Psychiatry, University of Pittsburgh, School of Medicine,  
Pennsylvania, USA.  
SO Journal of geriatric psychiatry and neurology, (1998 Winter) 11  
(4) 206-12. Ref: 59  
Journal code: 8805645. ISSN: 0891-9887.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
**General Review; (REVIEW)**  
(REVIEW, TUTORIAL)  
LA English  
FS Priority Journals  
EM 199906  
ED Entered STN: 19990628  
Last Updated on STN: 19990628  
Entered Medline: 19990615  
AB Behavioral disturbances are common in patients with dementia. Medical  
intervention is needed if, for example, these behaviors threaten a  
patient's safety or jeopardize his or her ability to perform activities of  
daily living. Typical antipsychotic agents are associated with  
troublesome adverse effects in the elderly (e.g., anticholinergic effects,  
extrapyramidal symptoms). Atypical antipsychotics have reduced potential  
to cause these types of side effects but are not free from side effects.  
Recently, there has been a greater focus on the use of antidepressants to  
treat behavioral disturbances in dementia. Among these, **selective  
serotonin reuptake inhibitors** have been  
studied more commonly due to their safety profile in the elderly.  
Citalopram, in particular, has demonstrated efficacy in improving  
dementia-related behavioral symptoms.

L8 ANSWER 2 OF 25 MEDLINE on STN  
AN 1999076212 MEDLINE  
DN PubMed ID: 9859115  
TI [Significance of hepatic cytochrome P450 enzymes for psychopharmacology].  
Die Bedeutung des hepatischen Cytochrom-P450-Systems für die  
Psychopharmakologie.  
AU Normann C; Hesslinger B; Bauer J; Berger M; Walden J  
CS Abteilung für Psychiatrie und Psychotherapie, Klinikum der  
Albert-Ludwigs-Universität, Freiburg.

SO Der Nervenarzt, (1998 Nov) 69 (11) 944-55. Ref: 146  
 Journal code: 0400773. ISSN: 0028-2804.  
 CY GERMANY: Germany, Federal Republic of  
 DT Journal; Article; (JOURNAL ARTICLE)  
     **General Review; (REVIEW)**  
     (REVIEW, TUTORIAL)  
 LA German  
 FS Priority Journals  
 EM 199902  
 ED Entered STN: 19990316  
     Last Updated on STN: 19990316  
     Entered Medline: 19990226  
 AB Nearly all psychotropic drugs are metabolized by hepatic cytochrome  
 P450-enzymes. In humans, there are 5 isoenzymes involved in this process.  
 The activity of these enzymes can be modulated by a number of commonly  
 used drugs, yielding potentially hazardous interactions. Most of the  
 recently introduced **selective serotonin**  
**reuptake inhibitors** are potent inhibitors of cytochrome  
 P450 enzymes. Thus, the plasma concentrations of tricyclic  
 antidepressants or clozapine might be elevated into toxic levels. In  
 contrast, carbamazepine induces most of the isoenzymes. This potentiates  
 the elimination of tricyclics and antipsychotics and might cause a serious  
 risk for the recurrence of depressive or psychotic symptoms. Moreover,  
 5-10% of the population are slow metabolizers of **CYP2D6**. This  
 group is prone to increased adverse effects of moderately dosed  
 medication. This review systematically points out the reported or  
 predicted pharmacokinetic drug interactions in psychopharmacology  
 focussing on clinical significance.

L8 ANSWER 3 OF 25 MEDLINE on STN  
 AN 1999032558 MEDLINE  
 DN PubMed ID: 9817620  
 TI Differences in interactions of **SSRIs**.  
 AU Brosen K  
 CS Department of Clinical Pharmacology, Institute of Medical Biology, Odense  
 University, Denmark.  
 SO International clinical psychopharmacology, (1998 Sep) 13 Suppl 5  
 S45-7. Ref: 3  
 Journal code: 8609061. ISSN: 0268-1315.  
 CY ENGLAND: United Kingdom  
 DT Journal; Article; (JOURNAL ARTICLE)  
     **General Review; (REVIEW)**  
     (REVIEW, TUTORIAL)  
 LA English  
 FS Priority Journals  
 EM 199901  
 ED Entered STN: 19990209  
     Last Updated on STN: 19990209  
     Entered Medline: 19990128  
 AB The **SSRIs** differ from each other with regard to their chemical  
 structure, their pharmacokinetics and their potential for causing  
 pharmacokinetic interactions through inhibition of species of the  
 cytochrome P450 enzyme system. Cytochrome P450 (CYP) is a group of more  
 than 30 different heme containing proteins in humans, some of which play a  
 key role in the oxidation and hence the elimination of numerous drugs,  
 including the **SSRIs**. Thus fluvoxamine, but not citalopram,  
 fluoxetine, paroxetine and sertraline is a potent inhibitor of CYP1A2.  
 Accordingly fluvoxamine has interactions with other drugs eliminated by  
 CYP1A2 including caffeine, clozapine, olanzapine, theophylline,  
 propranolol and tacrine. CYP2C19 is the source of the S-mephenytoin  
 oxidation polymorphism. About 2% of whites are poor metabolizers in whom  
 CYP2C19 is not expressed. Poor metabolizers have an impaired elimination  
 of among other drugs citalopram. Although not metabolized by CYP2C19,  
 fluvoxamine is still a potent inhibitor of the enzyme. The same applies  
 to fluoxetine. **CYP2D6** only makes up about 2-5% of the total  
 P450 in the human liver, but anyway is the major enzyme catalyzing more  
 than 30 clinically used drugs including all of the tricyclic  
 antidepressants, several neuroleptics, opiates, betablockers,  
 antiarrhythmics and among the **SSRIs** N-desmethylocitalopram,

fluvoxamine, fluoxetine and paroxetine but not sertraline. All of the **SSRIs** inhibit **CYP2D6** but fluoxetine, norfluoxetine and paroxetine are particularly potent inhibitors. CYP3A4 is the most abundant human cytochrome P450, but most of the **SSRIs** with the exception of norfluoxetine do not inhibit this enzyme, and interactions with **SSRIs** and CYP3A4 appear not to be a significant.

L8 ANSWER 4 OF 25 MEDLINE on STN  
AN 1999032557 MEDLINE  
DN PubMed ID: 9817619  
TI Care of depression in the elderly: comparative pharmacokinetics of **SSRIs**.  
AU Baumann P  
CS University Department of Adult Psychiatry, Prilly-Lausanne, Switzerland.  
SO International clinical psychopharmacology, (1998 Sep) 13 Suppl 5  
S35-43. Ref: 58  
Journal code: 8609061. ISSN: 0268-1315.  
CY ENGLAND: United Kingdom  
DT Journal; Article; (JOURNAL ARTICLE)  
General Review; (REVIEW)  
(REVIEW, TUTORIAL)  
LA English  
FS Priority Journals  
EM 199901  
ED Entered STN: 19990209  
Last Updated on STN: 19990209  
Entered Medline: 19990128  
AB Citalopram, fluoxetine, fluvoxamine, paroxetine and sertraline are the selective serotonin reuptake inhibiting antidepressants available. They differ by their chemical structure, metabolism and pharmacokinetics. Cytochrome P-450 of the liver plays an important role in their metabolism, but CYP1A2, CYP2C19, **CYP2D6**, CYP3A4 and possibly some other isoforms differ by their relative contribution. Citalopram and fluoxetine are available as racemic compounds: stereospecificity of their enantiomers has been shown for their serotonergic pharmacology, metabolism and kinetics. The pharmacokinetics of drugs may be modified in elderly patients, at different levels: absorption, distribution, metabolism and excretion. In these patients, depending on the **selective serotonin reuptake inhibitor (SSRI)** used, it is recommended to adapt the dose of the antidepressant: Lower doses should be used for citalopram, paroxetine and probably also for sertraline, when therapy is initiated. No clear evidence was found for fluoxetine and fluvoxamine concerning an age dependent metabolism. As elderly depressive patients may also suffer from somatic diseases, this should be considered in the choice of the dose of an **SSRI**, as for some of them, elimination is decreased in hepatic (citalopram, fluoxetine, fluvoxamine, sertraline) or renal (paroxetine) impairments.

L8 ANSWER 5 OF 25 MEDLINE on STN  
AN 1999000246 MEDLINE  
DN PubMed ID: 9786307  
TI Drug interactions with newer antidepressants: role of human cytochromes P450.  
CM Comment in: J Clin Psychiatry. 2000 Feb;61(2):144. PubMed ID: 10732663  
AU Greenblatt D J; von Moltke L L; Harmatz J S; Shader R I  
CS Department of Pharmacology and Experimental Therapeutics, Tufts University School of Medicine and New England Medical Center, Boston, Mass 02111, USA.. Dgreenblatt@Infonet.tufts.edu  
NC MH-19924 (NIMH)  
MH-34223 (NIMH)  
RR-00054 (NCRR)  
+  
SO Journal of clinical psychiatry, (1998) 59 Suppl 15 19-27. Ref: 125  
Journal code: 7801243. ISSN: 0160-6689.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
General Review; (REVIEW)  
(REVIEW, TUTORIAL)

LA English  
FS Priority Journals  
EM 199810  
ED Entered STN: 19990106  
Last Updated on STN: 20000728  
Entered Medline: 19981027  
AB **Selective serotonin reuptake inhibitors** and related antidepressant compounds have the secondary pharmacologic property of inhibiting the activity of human cytochrome P450 enzymes responsible for the oxidative metabolism of many drugs. A number of clinically important pharmacokinetic drug interactions are a consequence of these cytochrome inhibiting effects. This review evaluates the clinical implications of the metabolic profiles of the newer antidepressants, the relative activities of various new antidepressants as inhibitors of human cytochrome P450, and the various in vivo and in vitro methodologies that can be used for identification and quantification of drug interactions.

L8 ANSWER 6 OF 25 MEDLINE on STN  
AN 1998259637 MEDLINE  
DN PubMed ID: 9597349  
TI New antidepressants and the cytochrome P450 system: focus on venlafaxine, nefazodone, and mirtazapine.  
AU Owen J R; Nemeroff C B  
CS Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, Georgia 30322, USA.  
NC MH-51761 (NIMH)  
SO Depression and anxiety, (1998) 7 Suppl 1 24-32. Ref: 40  
Journal code: 9708816. ISSN: 1091-4269.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
**General Review; (REVIEW)**  
(REVIEW, TUTORIAL)

LA English  
FS Priority Journals  
EM 199808  
ED Entered STN: 19980817  
Last Updated on STN: 20030204  
Entered Medline: 19980804  
AB **OBJECTIVE:** This review critically evaluates recent information on the cytochrome P450 system, with an emphasis on drug interactions involving antidepressant medications, particularly venlafaxine, nefazodone, and mirtazapine. **METHODS:** International literature on the cytochrome P450 system and related drug interactions from 1995-1997 were critically examined. **RESULTS:** Venlafaxine, nefazodone, and mirtazapine have different effects on the cytochrome P450 system. In vitro, venlafaxine is a weaker **CYP2D6** inhibitor than most of the **selective serotonin reuptake inhibitors (SSRIs)** by a factor of 1-3 orders of magnitude. In vivo drug interaction studies generally confirm in vitro results. However, some exceptions exist. The clinical significance of such interactions remains unknown. Venlafaxine had minimal or no demonstrable inhibition of CYP1A2, CYP3A4, or CYP2C. Nefazodone is a potent inhibitor of CYP3A4 and is therefore absolutely contraindicated with concurrent administration of terfenadine, astemizole, and cisapride. It is a weak inhibitor of CYP1A2, 3A4, and 2D6. A metabolite of nefazodone, mCPP, is a weak and probably clinically insignificant inhibitor of **CYP2D6**. Mirtazapine has minimal inhibitory effects on CYP1A2, CYP3A4, and **CYP2D6** in vitro. Little is known about its interactions with other drugs. **CONCLUSIONS:** With the addition of the latest antidepressant medications, the clinician may now choose antidepressants with little liability for drug-drug interactions. Venlafaxine and mirtazapine are associated with a lower risk of clinically significant drug interactions than **SSRIs**. Nefazodone is a potent inhibitor of CYP3A4 and therefore may not be suitable for all patient populations. It is, however, a much weaker **CYP2D6** inhibitor than the **SSRIs**. More studies are needed to assess more accurately and precisely the risk of such untoward drug-drug interactions with these novel antidepressants, particularly in more diverse ethnic patient populations.



L8 ANSWER 7 OF 25 MEDLINE on STN  
 AN 1998232792 MEDLINE  
 DN PubMed ID: 9571301  
 TI Metabolism of the newer antidepressants. An overview of the pharmacological and pharmacokinetic implications.  
 AU Caccia S  
 CS Istituto di Ricerche Farmacologiche Mario Negri, Milan, Italy..  
 caccia@irfmm.mnegri.it  
 SO Clinical pharmacokinetics, (1998 Apr) 34 (4) 281-302. Ref: 157  
 Journal code: 7606849. ISSN: 0312-5963.  
 CY New Zealand  
 DT Journal; Article; (JOURNAL ARTICLE)  
 General Review; (REVIEW)  
 (REVIEW, TUTORIAL)  
 LA English  
 FS Priority Journals  
 EM 199806  
 ED Entered STN: 19980611  
 Last Updated on STN: 19980611  
 Entered Medline: 19980604  
 AB Several chemically unrelated agents has been developed and introduced in the past decade, to supplement the earlier antidepressants. These include inhibitors of the reuptake of serotonin [the **selective serotonin reuptake inhibitors (SSRI)**]] or noradrenaline (reboxetine) or both (milnacipran and venlafaxine), as well as drugs with distinct neurochemical profiles such as mirtazapine, nefazodone, moclobemide and tianeptine. Like the earlier drugs, these newer antidepressants are almost totally biotransformed before excretion, except for milnacipran whose clearance appears to be due equally to both urinary excretion and metabolism. Sometimes--as in the case of moclobemide--up to 20 metabolites have been identified in body fluids. In some cases, however, only a few metabolites have been detected, and a substantial proportion of the dose remains unaccounted for (e.g. fluoxetine and fluvoxamine). Metabolism generally proceeds through sequential or parallel oxidative pathways. These may be affected to varying degrees by physiological and pathological factors and those mediated by cytochrome P450 (CYP) 2D6 and CYP2C19 through genetic polymorphism. Some are influenced by chirality (e.g. the dealkylation of citalopram and fluoxetine), although information on this aspect of disposition is still lacking for other drugs existing as racemates (e.g. mirtazapine and tianeptine) and milnacipran, which is probably a mixture of 4 stereoisomers. Others again are saturable within the therapeutic range of doses (e.g. some pathways of metabolism of fluoxetine, fluvoxamine, nefazodone, paroxetine and venlafaxine). This may explain the individual variability with all these drugs which, from the pharmacokinetic point of view, is the same as with tricyclic agents. Our knowledge of the isoenzymes involved in the various oxidation pathways and their relevance for potential drug interactions varies from a considerable amount for most of the **SSRI** and nefazodone, to minimal for reboxetine and tianeptine. This information is useful for predicting the pharmacokinetic interactions mediated through inhibition of specific isoenzymes. This would be better appreciated if the enzymatic mechanisms involved in the biotransformation of the metabolite(s), and their role in drug interactions, were also known. This information is still lacking for some drugs, although metabolites may exhibit in vitro inhibitory potencies of similar to (paroxetine and its M2 metabolite as inhibitors of **CYP2D6**) or even greater than that of the parent drug (norfluoxetine is more potent than fluoxetine as an inhibitor of CYP3A3/4, and in view of the longer half-life ( $t_{1/2}$ ) of the metabolite the potential for interactions may persist for weeks after discontinuation of the parent drug). While we do know something about the biological activity of the metabolites of some of these drugs, we know very little about others. With few exceptions this knowledge refers only to the major metabolite(s) and regards the main in vitro effects as exerted by the parent drug. However, in vitro potency and selectivity may not translate directly into in vivo, and either major or minor metabolites may have characteristic in vitro and in vivo properties. For example, unlike the parent drug some minor ring-opened metabolites of moclobemide have monoamine oxidase-B

inhibitory activity in the rat, and the nefazodone metabolite m-chlorophenyl-piperazine shows activity on 5-HT<sub>2C</sub> receptors in rats and humans. Data on the brain-to-blood partition of metabolites compared with their parent drug are available only in a few cases. They are still not known for the main metabolites of fluvoxamine, milnacipran, mirtazapine, moclobemide, nefazodone, paroxetine, reboxetine and venlafaxine, despite the fact that total blood concentrations do not always reflect the metabolite: parent drug ratio in brain. Thus, in most cases, we do not really know what part hepatic metabolism plays in the overall effect of the administered parent drug.

L8 ANSWER 8 OF 25 MEDLINE on STN  
AN 1998098324 MEDLINE  
DN PubMed ID: 9435993  
TI **Selective serotonin reuptake inhibitors** and CNS drug interactions. A critical review of the evidence.  
AU Sproule B A; Naranjo C A; Brenner K E; Hassan P C  
CS Psychopharmacology Research Program, Sunnybrook Health Science Centre, Toronto, Ontario, Canada.  
SO Clinical pharmacokinetics, (1997 Dec) 33 (6) 454-71. Ref: 106  
Journal code: 7606849. ISSN: 0312-5963.  
CY New Zealand  
DT Journal; Article; (JOURNAL ARTICLE)  
General Review; (REVIEW)  
(REVIEW, ACADEMIC)  
LA English  
FS Priority Journals  
EM 199802  
ED Entered STN: 19980217  
Last Updated on STN: 19980217  
Entered Medline: 19980205  
AB The potential for drug-drug interactions in psychiatric patients is very high as combination psychopharmacotherapy used to treat comorbid psychiatric disorders, to treat the adverse effects of a medication, to augment a medication effect or to treat concomitant medical illnesses. Interactions can be pharmacodynamic or pharmacokinetic in nature. This paper focuses on the metabolic kinetic interactions between **selective serotonin reuptake inhibitors (SSRIs)** and other central nervous system (CNS) drugs. The evidence for and clinical significance of these interactions are reviewed, with special emphasis on antipsychotics, tricyclic antidepressants and benzodiazepines. Many psychotropic medications have an affinity for the cytochrome P450 (CYP) enzymes which promote elimination by transforming lipid soluble substances into more polar compounds. **SSRIs** serve both as substrates and inhibitors of these enzymes. In vitro studies provide a screening method for evaluating drug affinities for substrates, inhibitors or inducers of CYP enzymes. Although in vitro data are important as a starting point for predicting these metabolic kinetic drug interactions, case reports and controlled experimental studies in humans are required to fully evaluate their clinical significance. Several factors must be considered when evaluating the clinical significance of a potential interaction including: (a) the nature of each drug's activity at an enzyme site (substrate, inhibitor or inducer); (b) the potency estimations for the inhibitor/inducer; (c) the concentration of the inhibitor/inducer at the enzyme site; (d) the saturability of the enzyme; (e) the extent of metabolism of the substrate through this enzyme (versus alternative metabolic routes); (f) the presence of active metabolites of the substrate; (g) the therapeutic window of the substrate; (h) the inherent enzyme activity of the individual, phenotyping/genotyping information; (i) the level of risk of the individual experiencing adverse effects (e.g. the elderly) and (j) from an epidemiological perspective, the probability of concurrent use. This paper systematically reviews both the in vitro and in vivo evidence for drug interactions between **SSRIs** and other CNS drugs. As potent inhibitors of **CYP2D6**, both paroxetine and fluoxetine have the potential to increase the plasma concentrations of antipsychotic medications metabolised through this enzyme, including perphenazine, haloperidol, thioridazine and risperidone in patients who

are **CYP2D6** extensive metabolisers. Controlled studies have demonstrated this for perphenazine with paroxetine and haloperidol with fluoxetine. Fluvoxamine, as a potent inhibitor of CYP1A2, can inhibit the metabolism of clozapine, resulting in higher plasma concentrations. Drug interactions between the **SSRIs** and tricyclic antidepressants (TCAs) can occur. Fluoxetine and paroxetine, as potent inhibitors of **CYP2D6**, can increase the plasma concentrations of secondary and tertiary tricyclic antidepressants. Sertraline and citalopram are less likely to have this effect. Fluvoxamine can increase the plasma concentrations of tertiary TCAs. Fluvoxamine inhibits, via CYP3A, CYP2C19 and CYP1A2, the metabolism of several benzodiazepines, including alprazolam, bromazepam and diazepam. Fluoxetine increases the plasma concentrations of alprazolam and diazepam by inhibiting CYP3A and CYP2C19, respectively. The clinical importance of the interaction with diazepam is attenuated by the presence of its active metabolite. Sertraline inhibits these enzymes only mildly to moderately at usual therapeutic doses. Therefore the potential for interactions is less; however, the in vivo evidence is minimal. Paroxetine and citalopram are unlikely to cause interactions with benzodiazepines. The evidence is conflicting for an interaction between carbamazepine and the **SSRIs** fluoxetine and fluvoxamine. These combinations should be used cautiously, and be accompanied by monitoring for adverse events and carb

L8 ANSWER 9 OF 25 MEDLINE on STN  
AN 1998091673 MEDLINE  
DN PubMed ID: 9429838  
TI Drug interactions of clinical significance with **selective serotonin reuptake inhibitors**.  
AU Mitchell P B  
CS School of Psychiatry, University of New South Wales, Sydney, Australia..  
phil.mitchell@unsw.edu.au  
SO Drug safety : an international journal of medical toxicology and drug experience, (1997 Dec) 17 (6) 390-406. Ref: 163  
Journal code: 9002928. ISSN: 0114-5916.  
CY New Zealand  
DT Journal; Article; (JOURNAL ARTICLE)  
General Review; (REVIEW)  
(REVIEW, TUTORIAL)  
LA English  
FS Priority Journals  
EM 199802  
ED Entered STN: 19980224  
Last Updated on STN: 20000303  
Entered Medline: 19980211  
AB The selective serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitors (**SSRIs**) have internationally become the accepted 'benchmark' class of antidepressants. It has become clear, however, that there are a number of clinically significant interactions between **SSRIs** and other medications. The most frequently described interactions are pharmacokinetic, which are far more prevalent than pharmacodynamic interactions. This article details those medications that may interact significantly with the **SSRIs**, and provides clinical guidelines for minimising the likelihood of such complications. The most common pharmacokinetic interactions are caused by an inhibitory effect of the **SSRIs** on the hepatic cytochrome P450 (CYP) metabolic system. The **SSRIs** differ in their potency in inhibiting a number of important CYP isoenzymes (CYP1A2, CYP2C9/10, CYP2C19, **CYP2D6** and CYP3A3/4). The major outcome of concern in relation to pharmacodynamic interactions is the development of the 'serotonin syndrome'. While combination of the **SSRIs** with the irreversible monoamine oxidase inhibitors is the most recognised cause of this syndrome, concurrent administration with moclobemide, tryptophan or selegiline (deprenyl) may also lead to a similar outcome.

L8 ANSWER 10 OF 25 MEDLINE on STN  
AN 97326259 MEDLINE  
DN PubMed ID: 9183126  
TI Pharmacology of the **selective serotonin reuptake inhibitors** in children and adolescents.



AU Leonard H L; March J; Rickler K C; Allen A J  
 CS Department of Psychiatry and Human Behavior, Brown University, Rhode  
 Island Hospital, Providence 02903, USA.  
 SO Journal of the American Academy of Child and Adolescent Psychiatry,  
 (1997 Jun) 36 (6) 725-36. Ref: 109  
 Journal code: 8704565. ISSN: 0890-8567.  
 CY United States  
 DT Journal; Article; (JOURNAL ARTICLE)  
 General Review; (REVIEW)  
 (REVIEW, TUTORIAL)  
 LA English  
 FS Priority Journals  
 EM 199707  
 ED Entered STN: 19970721  
 Last Updated on STN: 19970721  
 Entered Medline: 19970708  
 AB OBJECTIVE: To review the pharmacology of a new class of medications, the  
 potent **selective serotonin reuptake  
 inhibitors (SSRIs)**, what is known about their metabolism  
 in children and adolescents, and the practical clinical implications of  
 such. METHOD: Articles were retrieved through index Medicus searches for  
 articles published during the past 10 years on the **SSRIs** and on  
 pediatric pharmacology. RESULTS: More than 300 articles were reviewed.  
 Pharmacological data, derived from relevant adult literature, were  
 summarized and extrapolated to children and from the limited pediatric  
 literature. The **SSRIs** represent a new class of antidepressants  
 with distinct advantages in their side effect profile and their broad  
 therapeutic index over that seen with the tricyclic antidepressants.  
 Their advantage of few anticholinergic side effects and limited  
 cardiovascular toxicities are particularly relevant for the pediatric  
 population. The **SSRIs** are metabolized via the hepatic  
 cytochrome isoenzyme P450 system, and potential drug-drug interactions are  
 reviewed. CONCLUSIONS: The **SSRIs** appear to offer advantages  
 over the tricyclic antidepressants. Unfortunately, pharmacokinetic data  
 are lacking, and systematic studies of safety and efficacy in the  
 pediatric age group are limited. Preliminary reports are encouraging, but  
 further study is required.

L8 ANSWER 11 OF 25 MEDLINE on STN  
 AN 97221885 MEDLINE  
 DN PubMed ID: 9068931  
 TI Clinically relevant pharmacology of **selective serotonin  
 reuptake inhibitors**. An overview with emphasis on  
 pharmacokinetics and effects on oxidative drug metabolism.

AU Preskorn S H  
 CS Department of Psychiatry, University of Kansas School of Medicine,  
 Wichita, USA.  
 SO Clinical pharmacokinetics, (1997) 32 Suppl 1 1-21. Ref: 143  
 Journal code: 7606849. ISSN: 0312-5963.  
 CY New Zealand  
 DT Journal; Article; (JOURNAL ARTICLE)  
 General Review; (REVIEW)  
 (REVIEW, TUTORIAL)  
 LA English  
 FS Priority Journals  
 EM 199706  
 ED Entered STN: 19970620  
 Last Updated on STN: 19970620  
 Entered Medline: 19970609  
 AB This paper presents an overview of the clinically relevant pharmacology of  
**selective serotonin reuptake  
 inhibitors (SSRIs)** with an emphasis on their  
 pharmacokinetics and effects on cytochrome P450 (CYP) enzymes. The  
**SSRIs** are potent inhibitors of the neuronal reuptake pump for  
 serotonin (5-hydroxytryptamine; 5-HT) and have minimal effects on a number  
 of other sites of actions (e.g. neuroreceptors and fast sodium channels).  
 For this reason, drugs in this class have remarkable similarity as regards  
 acute and maintenance antidepressant efficacy and tolerability profile.  
 However, individual members of this class differ substantially in their

pharmacokinetics and effects on CYP enzymes. Most **SSRIs** have a half-life ( $t_{1/2}$ ) of approximately 1 day. Fluoxetine, however, has a longer  $t_{1/2}$  of 2 to 4 days, and its active metabolite, norfluoxetine, has an extended  $t_{1/2}$  of 7 to 15 days. Fluoxetine, paroxetine and, to a lesser extent, fluvoxamine inhibit their own metabolism. That is not the case for citalopram or sertraline. There are nonlinear increases in paroxetine plasma concentrations with dosage increases, but proportional changes with citalopram and sertraline. Indirect data suggest that fluoxetine and fluvoxamine also have nonlinear pharmacokinetics over their usual dosage range. Age-related increases in plasma drug concentrations for citalopram (approximately 130%) and paroxetine (approximately 50 to 100%) have been observed in healthy elderly (65 to 75 years) persons versus those who are younger. There is an age-gender interaction for sertraline, with its plasma concentrations being 35 to 40% lower in young men than in elderly or young females or elderly males. While there is no apparent change in fluvoxamine plasma levels as a function of age, plasma drug concentrations are 40 to 50% lower in males than in females. Limited data from clinical trials suggest that age-related differences with fluoxetine may be comparable to those of citalopram and paroxetine. Marked differences exist between the **SSRIs** with regard to effects on specific CYP enzymes and, thus, the likelihood of clinically important pharmacokinetic drug-drug interactions. The most extensive in vitro and in vivo research has been done with fluoxetine, fluvoxamine and sertraline; there has been less with paroxetine and citalopram. The available in vivo data at each drug's usually effective antidepressant dose are summarised below. Citalopram produces mild inhibition of **CYP2D6**. Fluvoxamine produces inhibition (which would be expected to be clinically meaningful) of two CYP enzymes. CYP1A2 and CYP2C19, and probably a third, CYP3A3/4. Fluoxetine substantially inhibits **CYP2D6** and probably CYP2C9/10, moderately inhibits CYP2C19 and mildly inhibits CYP3A3/4. Paroxetine substantially inhibits **CYP2D6** but does not appear to inhibit any other CYP enzyme. Sertraline produces mild inhibition of **CYP2D6** but has little, if any, effect on CYP1A2, CYP2C9/10, CYP2C19 or CYP3A3/4. Understanding the similarities and differences in the pharmacology of **SSRIs** can aid the clinician in optimal use of this important class of antidepressants.

ANSWER 12 OF 25 MEDLINE on STN

97184042 MEDLINE

PubMed ID: 9032002

Pharmacokinetic drug interaction potential of **selective serotonin reuptake inhibitors**.

Erratum in: Int Clin Psychopharmacol 1997 Mar;12(2):126

Lane R M

Pfizer, Inc., New York, NY 10017, USA.

International clinical psychopharmacology, (1996 Dec) 11 Suppl 5 31-61. Ref: 266

Journal code: 8609061. ISSN: 0268-1315.

ENGLAND: United Kingdom

Journal; Article; (JOURNAL ARTICLE)

**General Review; (REVIEW)**

(REVIEW, ACADEMIC)

English

Priority Journals

199705

Entered STN: 19970602

Last Updated on STN: 19980206

Entered Medline: 19970522

Obsessive-compulsive disorder (OCD) is a chronic disorder requiring long-term treatment. The pharmacological management of the disorder, therefore, requires the use of agents which, in addition to being efficacious and well tolerated, are unlikely to cause pharmacokinetic drug-drug interactions with concomitantly administered medication which the patient is receiving or may receive in the future. The

**selective serotonin reuptake**

**inhibitors (SSRIs)** have similar pharmacodynamic profiles

but their pharmacokinetic profiles are very different. Perhaps the most substantial pharmacokinetic difference among these drugs is in their potential for drug-drug interactions via the inhibition of cytochrome P450

(CYP) isoenzymes. This review provides comprehensive background information on these enzyme systems and discusses their significance with respect to the optimal care of patients. Fluoxetine is a substantial inhibitor of **CYP2D6**, has mild effects on CYP3A3/4, and may also have effects on CYP2C9/10 and CYP2C19. Effects on drugs metabolized by these enzymes can persist for many weeks after fluoxetine discontinuation due to the long half-life of fluoxetine and its active metabolite norfluoxetine. Fluvoxamine is a substantial inhibitor of CYP1A2 and CYP2C19, and a moderate inhibitor of CYP3A3/4. Paroxetine is a substantial inhibitor of **CYP2D6**. In contrast, sertraline and citalopram are mild inhibitors of **CYP2D6** at their usually effective doses and are not known to produce clinically meaningful inhibition of any other isoenzymes. However, citalopram has not been well studied against all of these enzymes, especially in vivo. An increased risk of pharmacokinetic drug interactions is the immediate clinical consequence of the inhibitory effects of these drugs on CYP isoenzymes. However, with the emphasis on long-term treatment, particularly in chronic conditions such as OCD, it will also be important to determine the long-term clinical consequences of substantially inhibiting specific CYP isoenzymes with those **SSRIs** which have these effects. Thus knowledge of the substrates and inhibitors of CYP isoenzymes may help clinicians to anticipate and avoid pharmacokinetic drug interactions and may better define rational prescribing practices.

L8 ANSWER 13 OF 25 MEDLINE on STN  
 AN 97123410 MEDLINE  
 DN PubMed ID: 8968657  
 TI Pharmacokinetic-pharmacodynamic relationship of the **selective serotonin reuptake inhibitors**.  
 AU Baumann P  
 CS Department Universitaire de Psychiatrie Adulte, Prilly-Lausanne, Switzerland.. Pierre.Baumann@inst.hospvd.ch  
 SO Clinical pharmacokinetics, (1996 Dec) 31 (6) 444-69. Ref: 191  
 Journal code: 7606849. ISSN: 0312-5963.  
 CY New Zealand  
 DT Journal; Article; (JOURNAL ARTICLE)  
 General Review; (REVIEW)  
 (REVIEW, TUTORIAL)  
 LA English  
 FS Priority Journals  
 EM 199703  
 ED Entered STN: 19970327  
 Last Updated on STN: 19970327  
 Entered Medline: 19970320  
 AB The recently introduced antidepressants, the **selective serotonin reuptake inhibitors (SSRIs)** ) [citalopram, fluoxetine, fluvoxamine, paroxetine and sertraline], are known for their clinical efficacy, good tolerability and relative safety. They differ from each other in chemical structure, metabolism and pharmacokinetic properties. Therapeutic drug monitoring of these compounds is not widely used, as the plasma concentration ranges within which clinical response with minimal adverse effects appears to be optimal are not clearly defined. Almost all recent assays developed for the quantitative determination of **SSRIs** and their metabolites in blood are based either on the separation of **SSRIs** by high performance liquid chromatography (HPLC) or gas chromatography (GC). Citalopram and fluoxetine have been introduced as racemic compounds. There are some differences in the pharmacological profile, metabolism and pharmacokinetics between the enantiomers of the parent compounds and their demethylated metabolites. Stereoselective chromatographic methods for their analysis in blood are now available. With regard to the **SSRIs** presently available, no clearcut plasma concentration-clinical effectiveness relationship in patients with depression has been shown, nor any threshold which defines toxic concentrations. This may be explained by their low toxicity and use at dosages where serious adverse effects do not appear. **SSRIs** vary widely in their qualitative and quantitative interaction with cytochrome P450 (CYP) isozymes in the liver. **CYP2D6** is inhibited by **SSRIs**, in order of decreasing potency paroxetine, norfluoxetine, fluoxetine, sertraline,

citalopram and fluvoxamine. This may have clinical consequences with some but not all **SSRIs**, when they are taken with tricyclic antidepressants. Except for citalopram and paroxetine, little is known about the enzymes which control the biotransformation of the **SSRIs**. There have been many reports on marked pharmacokinetic interactions between fluoxetine and tricyclic antidepressants. Fluoxetine has a stronger effect on their hydroxylation than on their demethylation. Interactions observed between fluoxetine and alprazolam, midazolam and carbamazepine seem to occur on the level of CYP3A. Fluvoxamine strongly inhibits the N-demethylation of some tricyclic antidepressants of the tertiary amine type and of clozapine. This may lead to adverse effects but augmentation with fluvoxamine can also improve response in very rapid metabolisers, as it increases the bioavailability of the comedication. Fluvoxamine inhibits with decreasing potency, CYP1A2, CYP2C19, **CYP2D6** and CYP1A1, but it is also an inhibitor of CYP3A. Fluoxetine and fluvoxamine have shown to increase methadone plasma concentrations in dependent patients. Some authors warn about a combination of monoamine oxidase (MAO) inhibitors with **SSRIs**, as this could lead to a serotonergic syndrome. Studies with healthy volunteers suggest, however, that a combination of moclobemide and **SSRIs**, such as fluvoxamine, should not present serious risks in promoting a serotonin syndrome. A combination of moclobemide and fluvoxamine has successfully been used in refractory depression, but more studies are needed, including plasma-concentration monitoring, before this combined treatment can be recommended. Paroxetine is a substrate of **CYP2D6**, but other enzyme(s) could also be involved. Its pharmacokinetics are linear in poor metabolisers of sparteine, and non-linear in extensive metabolisers. Due to its potent **CYP2D6** inhibiting properties, comedication with this **SSRI** can lead to an increase of tricyclic antidepressants in plasma, as shown with amitriptyline and trimipramine. CYP3A has been claimed to be involved in the biotransformation of sertraline to norsertraline. Clinical investigations (with desipramine) confirmed in vitro findings that **CYP2D6** inhibition by sertraline is only moderate. (ABSTRACT TRUNCATED)

L8 ANSWER 14 OF 25 MEDLINE on STN  
AN 97083694 MEDLINE  
DN PubMed ID: 9118585  
TI Pharmacokinetic changes in the elderly. Do they contribute to drug abuse and dependence?.  
AU Ozdemir V; Fourie J; Busto U; Naranjo C A  
CS Psychopharmacology Research Program, Sunnybrook Health Science Centre, University of Toronto, Ontario, Canada.  
SO Clinical pharmacokinetics, (1996 Nov) 31 (5) 372-85. Ref: 144  
Journal code: 7606849. ISSN: 0312-5963..  
CY New Zealand  
DT Journal; Article; (JOURNAL ARTICLE)  
General Review; (REVIEW)  
(REVIEW, ACADEMIC)  
LA English  
FS Priority Journals  
EM 199704  
ED Entered STN: 19970506  
Last Updated on STN: 19980206  
Entered Medline: 19970422  
AB The elderly frequently use psychoactive drugs including alcohol (ethanol), benzodiazepines and opioid analgesics, which have a propensity to cause abuse and dependence. Theoretically, the changes in pharmacokinetics of these agents in the elderly may modify their abuse and dependence potential. In the elderly, blood alcohol concentrations following an oral dose are higher, alcohol withdrawal syndrome follows a more severe and protracted clinical course and requires treatment with higher doses of chlordiazepoxide than needed for younger adults. However, there is no direct evidence that supports an increased direct abuse and dependence potential of alcohol because of its altered kinetics in the elderly. In the case of oxidatively metabolised benzodiazepine, both age-related pharmacokinetics and pharmacodynamic changes may increase their clinical effects in the elderly. The hypothesis that benzodiazepines have an



increased abuse and dependence potential in the elderly has not been tested. Many of the benzodiazepines (e.g. alprazolam, triazolam and midazolam) are metabolised by the cytochrome P450 (CYP)3A subfamily. The pharmacokinetics of these agents may be modified by inhibition of CYP3A due to concurrently administered medications such as **selective serotonin reuptake inhibitors**. Unfortunately, data on the direct measures of abuse and dependence potential of benzodiazepines are not available in the elderly. Thus, a conclusive statement on the contribution of age-related pharmacokinetic changes to benzodiazepine abuse and dependence cannot be made at the present time. The clinical effects of codeine do not appear to change with age. Codeine is O-demethylated to its active metabolite morphine by the genetically polymorphic **CYP2D6** isozyme. The activity of this isozyme is unaltered by age, gender or smoking habits; however, it is subject to potent inhibition by some of the frequently used medications in the elderly, such as the antidepressants paroxetine and fluoxetine. This may result in an impairment in O-demethylation of codeine to morphine and may lead to a decrease in the abuse and dependence potential of codeine. Conversely, those with a very rapid **CYP2D6** catalytic activity may have an increased potential for codeine abuse and dependence. The clinical significance of age-related pharmacokinetic changes should be evaluated within the context of clinical practice. Most physicians are inclined to prescribe lower doses to the elderly, which may offset the potential impact of altered pharmacokinetics on the abuse and dependence potential of psychoactive agents. In summary, the available data are not sufficient for a definitive conclusion on whether the pharmacokinetic changes in the elderly translate to an increase in the abuse and dependence potential of alcohol, benzodiazepines or opioids. In particular, the data on age-associated changes in direct measures of abuse potential of these agents are missing. Future comparative systemic pharmacokinetic-pharmacodynamic studies assessing pertinent outcome measures on abuse and dependence potential of commonly used psychoactive drugs are required to resolve the ongoing controversy on risk factors for drug abuse and dependence in the elderly.

L8 ANSWER 15 OF 25 MEDLINE on STN  
 AN 97054151 MEDLINE  
 DN PubMed ID: 8898530  
 TI Clinical importance of genetic polymorphism of drug oxidation.  
 AU Edeki T  
 CS Department of Medicine, Meharry Medical College, Nashville, Tennessee 37208, USA.  
 NC FD-T 000888 (FDA)  
 SO Mount Sinai journal of medicine, New York, (1996 Oct-Nov) 63 (5-6) 291-300. Ref: 134  
 Journal code: 0241032. ISSN: 0027-2507.  
 CY United States  
 DT Journal; Article; (JOURNAL ARTICLE)  
 General Review; (REVIEW)  
 (REVIEW, TUTORIAL)  
 LA English  
 FS Priority Journals  
 EM 199612  
 ED Entered STN: 19970128  
 Last Updated on STN: 19970128  
 Entered Medline: 19961213  
 AB Certain individuals have a metabolic deficiency in the metabolism of debrisoquin, sparteine, dextromethorphan, and more than 80 other clinically important drugs. Examples of such drugs include tricyclic antidepressants, neuroleptics, **selective serotonin reuptake inhibitors**, beta-adrenoceptor blockers, and antiarrhythmics. **CYP2D6**, the enzyme responsible for the metabolism of these drugs, is polymorphically distributed in different populations. Studies in different ethnic groups in particular demonstrate significant variation. **CYP2D6** deficiency has important therapeutic consequences, such as increased side effects when medications that are substrates of this enzyme are prescribed for such individuals. To optimize drug therapy, physicians should therefore determine the metabolic capacity of their patients.



L8 ANSWER 16 OF 25 MEDLINE on STN  
 AN 97044835 MEDLINE  
 DN PubMed ID: 8889906  
 TI Cytochrome P450 enzymes: interpretation of their interactions with  
**selective serotonin reuptake**  
**inhibitors.** Part II.  
 AU Harvey A T; Preskorn S H  
 CS Psychiatric Research Institute, Wichita, KS 67214-2878, USA.  
 SO Journal of clinical psychopharmacology, (1996 Oct) 16 (5)  
 345-55. Ref: 107  
 Journal code: 8109496. ISSN: 0271-0749.  
 CY United States  
 DT Journal; Article; (JOURNAL ARTICLE)  
**General Review; (REVIEW)**  
 (REVIEW, TUTORIAL)  
 LA English  
 FS Priority Journals  
 EM 199703  
 ED Entered STN: 19970321  
 Last Updated on STN: 19990129  
 Entered Medline: 19970311  
 AB The **SSRIs** have been used as an example to show how one might  
 interpret the available evidence to draw conclusions about the  
 relationships between drugs and P450s. Under what circumstances might one  
 apply the knowledge of such relationships? First, the clinical  
 implications must be considered when drugs with a narrow therapeutic index  
 are coprescribed with other drugs that may affect P450s. For example,  
 good clinical practice demands that before a TCA is coprescribed with  
 another drug, the physician be aware of the potential for the second drug  
 to interact with **CYP2D6**. Second, it may be helpful to consider  
 P450 enzymes when adverse events occur during polypharmacy. It may happen  
 that a known side effect of one drug occurs. Rather than attributing this  
 to patient sensitivity, the physician should consider the possibility that  
 a pharmacokinetic drug interaction increased plasma drug concentration,  
 which in turn enhanced the probability of such an occurrence. Even when a  
 pharmacokinetic drug interaction is considered as a possible cause, an  
 appreciation of the role of P450s may lead to the realization that an  
 interaction was not only possible but that it was likely. Finally,  
 copharmacy can be used intentionally to produce controlled interactions.  
 Indeed, planned pharmacokinetic drug interactions at the level of P450s  
 have been proposed to reduce cyclosporine dosage requirements, to reduce  
 variability of TCA levels, and to manipulate the contribution of  
 alternative metabolic pathways to minimize toxic effects. As long as  
 pharmaceuticals are metabolized by the P450 system, interactions with the  
 various isozymes will be inescapable. It is fortunate that understanding  
 them is becoming more tractable.

L8 ANSWER 17 OF 25 MEDLINE on STN  
 AN 97021767 MEDLINE  
 DN PubMed ID: 8868127  
 TI Metabolism of psychotropic drugs: pharmacological and clinical relevance.  
 AU Daniel W  
 CS Department of Pharmacokinetics and Drug Metabolism, Polish Academy of  
 Sciences, Krakow, Poland.  
 SO Polish journal of pharmacology, (1995 Sep-Oct) 47 (5) 367-79.  
 Ref: 132  
 Journal code: 9313882. ISSN: 1230-6002.  
 CY Poland  
 DT Journal; Article; (JOURNAL ARTICLE)  
**General Review; (REVIEW)**  
 (REVIEW, ACADEMIC)  
 LA English  
 FS Priority Journals  
 EM 199611  
 ED Entered STN: 19961219  
 Last Updated on STN: 19961219  
 Entered Medline: 19961127  
 AB Cytochrome P-450 (CYP) catalyzes phase I metabolic reactions of

psychotropic drugs. The main isoenzymes responsible for their biotransformation are CYP1A2, **CYP2D6**, CYP3A4 and these of the subfamily CYP2C. The majority of metabolites of psychotropic drugs are biologically active. Some of them retain pharmacological properties of parent compounds (eg. **selective serotonin reuptake inhibitors**, risperidone, carbamazepine, benzodiazepines), but others display quite different (eg. amitriptyline, buspirone) or even opposite (trazodone) profiles. They are present in vivo in concentrations high enough to contribute to pharmacological and clinical effects of the administered drugs. Active metabolites of psychotropics are also characterized by pharmacokinetic properties different from their parent compounds, e.g. half-life time, plasma protein binding, blood-brain-barrier penetration, the cerebrospinal fluid (CSF) protein binding and tissue binding. These properties lead, in turn, to differences in the brain/plasma and the CSF/plasma concentration ratios between a drug and its metabolites. Therefore studies relating a pharmacological or therapeutic response of psychotropic drug to its plasma concentrations should not disregard the presence of its active metabolites, considering their distinct pharmacological and pharmacokinetic properties. With regard to a low therapeutic index of psychotropics, interindividual differences in the rate of their metabolism, genetic polymorphism of their main metabolic pathways and metabolic interactions in clinical drug combinations, the phenotyping of patients at the beginning of therapy and a control of drug concentrations (and its active metabolites) at a steady state and during coadministration of another drug, may increase the efficiency and safety of the pharmacotherapy of psychiatric disorders.

L8 ANSWER 18 OF 25 MEDLINE on STN

AN 96440968 MEDLINE

DN PubMed ID: 8845855

TI The pharmacogenetics of codeine hypoalgesia.

AU Sindrup S H; Brosen K

CS Department of Clinical Pharmacology, Odense University, Denmark.

SO Pharmacogenetics, (1995 Dec) 5 (6) 335-46. Ref: 91

Journal code: 9211735. ISSN: 0960-314X.

CY ENGLAND: United Kingdom

DT Journal; Article; (JOURNAL ARTICLE)

**General Review; (REVIEW)**

(REVIEW, TUTORIAL)

LA English

FS Priority Journals

EM 199610

ED Entered STN: 19961106

Last Updated on STN: 19961106

Entered Medline: 19961024

AB Codeine is an old drug that is still widely used to treat mild and moderate pain. It is mainly metabolised by glucuronidation, but minor pathways are N-demethylation to norcodeine and O-demethylation to morphine. The latter pathway depends on the genetically polymorphic **CYP2D6** which is absent in 7% of the white population (PM) and present in the remainder (EM). Lack of influence of codeine on experimental pain in PM as well as in EM treated with the **CYP2D6** blocker quinidine, who are both practically unable to convert codeine to morphine, has supported an old hypothesis that codeine acts through metabolically formed morphine. Possibly, local codeine O-demethylation in the CNS is of major importance for its hypoalgesic effect. Such a local morphine formation from codeine, which supposedly is also catalysed by **CYP2D6**, could explain why the hypoalgesic effect of codeine stems from morphine despite relatively low plasma levels of morphine after standard hypoalgesic doses of codeine. Dependence of codeine hypoalgesia on morphine formation via **CYP2D6** makes this effect liable to interaction with drugs that are inhibitors of **CYP2D6**. Examples of potent inhibitors of **CYP2D6** are quinidine, some **selective serotonin reuptake inhibitors** and some neuroleptics. Less potent inhibitors, such as tricyclic antidepressants, will probably also reduce the pain relieving effect of codeine, since codeine has a low affinity for **CYP2D6**. Biosynthesis of morphine in humans may also include steps catalysed by

**CYP2D6.** Experimental studies in large groups of EM and PM indicate that this may lead to interphenotype differences in pain tolerance.

ANSWER 19 OF 25 MEDLINE on STN  
96335126 MEDLINE  
PubMed ID: 8698676  
Serotonin selective reuptake inhibitor drug interactions and the cytochrome P450 system.  
Ereshefsky L; Riesenman C; Lam Y W  
Clinical Pharmacy Programs, University of Texas Health Science Center, San Antonio State Hospital, USA.  
Journal of clinical psychiatry, (1996) 57 Suppl 8 17-24; discussion 25. Ref: 78  
Journal code: 7801243. ISSN: 0160-6689.  
United States  
Journal; Article; (JOURNAL ARTICLE)  
**General Review; (REVIEW)**  
(REVIEW, TUTORIAL)  
English  
Priority Journals  
199609  
Entered STN: 19960912  
Last Updated on STN: 19980206  
Entered Medline: 19960905  
The article focuses on the effects of the serotonin selective reuptake inhibitors (**SSRIs**) on specific drug metabolizing isoenzymes: **CYP2D6**, CYP3A3/4, CYP1A2, CYP2C9, and CYP2C19. Both in vitro and in vivo data regarding the inhibition potential of the **SSRIs** at each of these isoenzyme systems are reviewed. In general, the magnitude of the in vivo interactions between the **SSRIs** and substrates for these isoenzyme systems mirrors to a large extent their in vitro inhibitory potencies. However, in vitro work is limited owing to pharmacokinetic considerations, the effect of metabolites on the isoenzymes, and the likelihood that several isoenzymes are co-responsible for the metabolism of a substrate.

ANSWER 20 OF 25 MEDLINE on STN  
96301730 MEDLINE  
PubMed ID: 8732441  
Are pharmacokinetic drug interactions with the **SSRIs** an issue?.  
Erratum in: Int Clin Psychopharmacol 1996 Jun;11(2):153  
Broosen K  
Department of Clinical Pharmacology, Odense University, Denmark.  
International clinical psychopharmacology, (1996 Mar) 11 Suppl 1 23-7. Ref: 9  
Journal code: 8609061. ISSN: 0268-1315.  
ENGLAND: United Kingdom  
Journal; Article; (JOURNAL ARTICLE)  
**General Review; (REVIEW)**  
(REVIEW, TUTORIAL)  
English  
Priority Journals  
199610  
Entered STN: 19961022  
Last Updated on STN: 19980206  
Entered Medline: 19961009  
The development of the **selective serotonin reuptake inhibitors (SSRIs)** began 20 years ago, around the time when it was discovered that the cytochrome P450 system consists of multiple drug-metabolizing enzymes. There are 5-10 important drug-metabolizing P450 enzymes in the human liver, and their relationship with **SSRIs** has been studied intensively during the last 5 years. Thus, among the **SSRIs**, fluvoxamine is the only very potent inhibitor of cytochrome P4501A2 (CYP1A2). All of the **SSRIs** inhibit **CYP2D6** ('sparteine/debrisoquine oxygenase') but fluoxetine and paroxetine are clearly the most potent in this regard. Fluoxetine and fluvoxamine are moderate inhibitors of CYP2C19 ('S-mephenytoinhydroxylase'), and fluvoxamine might also be a

moderate inhibitor of CYP2C9. Thus, although much still has to be learned about **SSRIs** and cytochrome P450, it seems that citalopram and sertraline have the most favourable profile in relation to drug interactions.

L8 ANSWER 21 OF 25 MEDLINE on STN  
AN 96153679 MEDLINE  
DN PubMed ID: 8567194  
TI Cytochrome P450 monooxygenases and interactions of psychotropic drugs: a five-year update.  
AU Shen W W  
CS Saint Louis University School of Medicine, Missouri, USA.  
SO International journal of psychiatry in medicine, (1995) 25 (3) 277-90. Ref: 78  
Journal code: 0365646. ISSN: 0091-2174.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
**General Review; (REVIEW)**  
(REVIEW, TUTORIAL)  
LA English  
FS Priority Journals  
EM 199603  
ED Entered STN: 19960315  
Last Updated on STN: 19960315  
Entered Medline: 19960305  
AB OBJECTIVE: This article is a five-year update on a previous review article (International Journal of Psychiatry in Medicine, 21:47-56, 1991) on cytochrome P450 monooxygenases and interactions of psychotropic drugs. METHOD: In the literature review, the recent committee work on nomenclature of the P450 superfamily are highlighted. Then, the author reviewed gene clusters of three human cytochrome P450s--CYP1A2, **CYP2D6**, and CYP3A4 with the focus on the changes of serum levels of the coadministered psychotropic drugs in the context of enzymatic induction and inhibition of these three hepatic enzymes. RESULTS: As indicated in one table, the author stratified probes, inducers, inhibitors, chemical reactions, and substrates under these three gene clusters. As shown in another simple table, the author compared the hepatic enzymatic inhibitions of four **selective serotonin reuptake inhibitors** and pointed out the inhibition potentials of fluvoxamine at CYP1A2, fluoxetine and paroxetine at **CYP2D6**, and fluoxetine and fluvoxamine at CYP3A4 if these two **SSRIs** have higher serum concentrations. CONCLUSION: The author suggests that with these systematic approaches, this rapidly adding knowledge can help psychiatrists better understand psychotropic drug interactions and maximize the benefits of patients' psychopharmacotherapy.

L8 ANSWER 22 OF 25 MEDLINE on STN  
AN 96113414 MEDLINE  
DN PubMed ID: 8846618  
TI Antidepressant drug interactions and the cytochrome P450 system. The role of cytochrome P450 2D6.  
AU Ereshefsky L; Riesenman C; Lam Y W  
CS University of Texas Health Science Center, Clinical Pharmacy Programs, San Antonio 78284-6220, USA.  
SO Clinical pharmacokinetics, (1995) 29 Suppl 1 10-8; discussion 18-9. Ref: 38  
Journal code: 7606849. ISSN: 0312-5963.  
CY New Zealand  
DT Journal; Article; (JOURNAL ARTICLE)  
**General Review; (REVIEW)**  
(REVIEW, TUTORIAL)  
LA English  
FS Priority Journals  
EM 199610  
ED Entered STN: 19961106  
Last Updated on STN: 19961106  
Entered Medline: 19961024  
AB The **selective serotonin reuptake**

**inhibitors (SSRIs)** and venlafaxine display the following rank order of in vitro potency against the cytochrome P450 (CYP) isoenzyme **CYP2D6** as measured by their inhibition sparteine and/or dextromethorphan metabolism: paroxetine > fluoxetine identical to norfluoxetine > or = sertraline > or = fluvoxamine > venlafaxine. On this basis, paroxetine would appear to have the greatest and fluvoxamine and venlafaxine the least potential for drug interactions with **CYP2D6**-dependent drugs. In vivo, inhibitory potency is affected by the plasma concentration of the free (unbound) drug, a potentially important consideration since many **CYP2D6**-metabolised drugs exhibit nonlinear (saturable) kinetics, and by the presence of metabolites, which might accumulate and interact with the CYP system. Under steady-state conditions, paroxetine and fluoxetine are approximately clinically equipotent inhibitors of **CYP2D6** in vivo (as determined through their effects on desipramine metabolism); sertraline, in contrast, shows lower steady-state plasma concentrations than fluoxetine and, hence, a less pronounced inhibition of **CYP2D6**. Of the drugs that are metabolised by **CYP2D6**, secondary amine tricyclic antidepressants, antipsychotics (e.g. phenothiazines, and risperidone), codeine, some antiarrhythmics (e.g. flecainide) and beta-blockers form the focus of clinical attention with regard to their potential interactions with the **SSRIs**. Coadministration of desipramine and fluoxetine (20 mg/day) at steady-state produced an approximately 4-fold elevation in peak plasma desipramine concentrations, while the long half-life of the active metabolite norfluoxetine was responsible for a significant and long lasting (approximately 3 weeks) elevation of plasma desipramine concentrations after discontinuation of fluoxetine. Similarly, coadministration of desipramine with paroxetine produced an approximately 3-fold increase in plasma desipramine concentration. In contrast, coadministration of desipramine and sertraline (50 mg/day) for 4 weeks resulted in a considerably more modest (approximately 30%) elevation in plasma desipramine concentrations. Coadministration of fluoxetine (60 mg/day, as a loading dose) [equivalent to serum concentrations obtained with 20 mg/day at steady-state] with imipramine or desipramine resulted in approximately 3- to 4-fold increases in plasma area under the curve (AUC) values for both imipramine and desipramine (illustrating a significant drug interaction potential at multiple isoenzymes). Consistent with its minimal in vitro effect on **CYP2D6**, fluvoxamine shows minimal in vivo pharmacokinetic interaction with desipramine, but does interact with imipramine (approximately 3- to 4-fold increase in AUC) through inhibition of CYP3A3/4, CYP1A2, and CYP2C19. Thus, the extent of the in vivo interaction between the **SSRIs** and tricyclic antidepressants mirrors to a large extent their in vitro inhibitory potencies against **CYP2D6** and other isoenzyme systems, especially if one takes into account pharmacokinetic factors.

L8 ANSWER 23 OF 25 MEDLINE on STN  
 AN 96113413 MEDLINE  
 DN PubMed ID: 8846617  
 TI Overview of the pharmacokinetics of fluvoxamine.  
 AU van Harten J  
 CS Department of Clinical Pharmacology, Solvay Duphar BV, Weesp, The Netherlands.  
 SO Clinical pharmacokinetics, (1995) 29 Suppl 1 1-9. Ref: 49  
 Journal code: 7606849. ISSN: 0312-5963.  
 CY New Zealand  
 DT Journal; Article; (JOURNAL ARTICLE)  
 General Review; (REVIEW)  
 (REVIEW, TUTORIAL)  
 LA English  
 FS Priority Journals  
 EM 199610  
 ED Entered STN: 19961106  
 Last Updated on STN: 19961106  
 Entered Medline: 19961024  
 AB The pharmacokinetics of fluvoxamine, a **selective serotonin reuptake inhibitor (SSRI)** with antidepressant properties, are well established. After oral administration, the drug is almost completely absorbed from the



gastrointestinal tract, and the extent of absorption is unaffected by the presence of food. Despite complete absorption, oral bioavailability in man is approximately 50% on account of first-pass hepatic metabolism. Peak plasma fluvoxamine concentrations are reached 4 to 12 hours (enteric-coated tablets) or 2 to 8 hours (capsules, film-coated tablets) after administration. Steady-state plasma concentrations are achieved within 5 to 10 days after initiation of therapy and are 30 to 50% higher than those predicted from single dose data. Fluvoxamine displays nonlinear steady-state pharmacokinetics over the therapeutic dose range, with disproportionally higher plasma concentrations with higher dosages. Plasma fluvoxamine concentrations show no clear relationship with antidepressant response or severity of adverse effects. Fluvoxamine undergoes extensive oxidative metabolism, most probably in the liver. Nine metabolites have been identified, none of which are known to be pharmacologically active. The specific cytochrome P450 (CYP) isoenzymes involved in the metabolism of fluvoxamine are unknown. **CYP2D6**, which is crucially involved in the metabolism of paroxetine and fluoxetine, appears to play a clinically insignificant role in the metabolism of fluvoxamine. The drug is excreted in the urine, predominantly as metabolites, with only negligible amounts (< 4%) of the parent compound. Fluvoxamine shows a biphasic pattern of elimination with a mean terminal elimination half-life of 12 to 15 hours after a single oral dose; this is prolonged by 30 to 50% at steady-state. Plasma protein binding of fluvoxamine (77%) is low compared with that of other **SSRIs**. Fluvoxamine pharmacokinetics are substantially unaltered by increased age or renal impairment. However, its elimination is prolonged in patients with hepatic cirrhosis. Fluvoxamine inhibits oxidative drug metabolising enzymes (particularly CYP1A2, and less potently and much less potently CYP3A4 and **CYP2D6**, respectively) and has the potential for clinically significant drug interactions. Drugs whose metabolic elimination is impaired by fluvoxamine include tricyclic antidepressants (tertiary, but not secondary, amines), alprazolam, bromazepam, diazepam, theophylline, propranolol, warfarin and, possibly, carbamazepine. Fluvoxamine is a second generation antidepressant that selectively inhibits neuronal reuptake of serotonin (5-hydroxytryptamine; 5-HT). Fluvoxamine exhibits antidepressant activity similar to that of the tricyclic antidepressants, but has a somewhat improved tolerability profile, particularly with respect to a lower incidence of anticholinergic effects and reduced cardiotoxic potential. However, gastrointestinal adverse effects, especially nausea, are seen more frequently with fluvoxamine than with the tricyclic antidepressants. Fluvoxamine does not have an asymmetric carbon in its structure (fig. 1) and therefore does not exist as optical isomers. For this reason, the potentially confounding problem of stereoisomerism does not arise with fluvoxamine.

L8 ANSWER 24 OF 25 MEDLINE on STN  
AN 95348453 MEDLINE  
DN PubMed ID: 7622807  
TI Comparative pharmacokinetics of **selective serotonin reuptake inhibitors**: a look behind the mirror.  
AU Baumann P; Rochat B  
CS Unite de Biochimie et Psychopharmacologie Clinique, Departement Universitaire de Psychiatrie Adulte, Prilly-Lausanne, Switzerland.  
SO International clinical psychopharmacology, (1995 Mar) 10 Suppl 1 15-21. Ref: 61  
Journal code: 8609061. ISSN: 0268-1315.  
CY ENGLAND: United Kingdom  
DT Journal; Article; (JOURNAL ARTICLE)  
**General Review; (REVIEW)**  
(REVIEW, TUTORIAL)  
LA English  
FS Priority Journals  
EM 199508  
ED Entered STN: 19950911  
Last Updated on STN: 19990129  
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AB The presently available **selective serotonin reuptake inhibitors (SSRIs)** citalopram, fluoxetine, fluvoxamine, paroxetine and sertraline, despite their common

mechanism of action, differ in their chemical structure, metabolism and pharmacokinetics. From a clinical point of view, it is of relevance that potency to inhibit the cytochrome P450 isozyme **CYP2D6** gradually decreases from paroxetine, fluoxetine, norfluoxetine, desmethylocitalopram, fluvoxamine, and sertraline down to citalopram, explaining to a great extent differences in pharmacokinetic interactions between the **SSRIs** and tricyclic antidepressants, which are metabolized by this enzyme. Fluvoxamine interacts with these drugs by a mechanism involving inhibition of CYP1A2, CYP3A4, and CYP2C19. Except for paroxetine, a substrate of **CYP2D6**, little is known about the enzymes implicated in the metabolism of **SSRIs**. Fluoxetine and citalopram are used as racemic drugs. Data on the stereoselectivity of their enantiomers in the inhibition of serotonin (5-HT) uptake in the animal brain, also those available on their metabolism and kinetics in humans, are presented. It may be concluded that for routine therapeutic drug monitoring, the plasma level measurement of the enantiomers of citalopram and fluoxetine is probably of little relevance. However, for the study of the structure-activity relationship between these drugs and the cerebral 5-HT transporter, the stereochemical differences of these enantiomers should be considered. In this sense, the enantiomers of these drugs could represent a promising tool to increase present knowledge.

L8 ANSWER 25 OF 25 MEDLINE on STN  
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 DN PubMed ID: 7814357  
 TI Pharmacogenetics and drug metabolism of newer antidepressant agents.  
 CM Comment in: J Clin Psychiatry. 1996 May;57(5):223-7. PubMed ID: 8626354  
 AU DeVane C L  
 CS Department of Psychiatry and Behavioral Sciences, Medical University of  
 South Carolina, Charleston 29425-0742.  
 SO Journal of clinical psychiatry, (1994 Dec) 55 Suppl 38-45;  
 discussion 46-7. Ref: 86  
 Journal code: 7801243. ISSN: 0160-6689.  
 CY United States  
 DT Journal; Article; (JOURNAL ARTICLE)  
 General Review; (REVIEW)  
 (REVIEW, TUTORIAL)  
 LA English  
 FS Priority Journals  
 EM 199502  
 ED Entered STN: 19950217  
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 AB A wide variety of drugs are metabolized by the human cytochrome P450  
 system, including antidepressants such as tricyclic antidepressants and  
 serotonin selective reuptake inhibitors (**SSRIs**). Each P450  
 isoenzyme is the product of a separate gene; a number of genes have  
 multiple alleles that result in genetic polymorphism in the population.  
 Both **CYP2D6** and CYP2C gene families are polymorphic; both  
 families are important in antidepressant metabolism. A number of  
 polymorphisms result in dysfunctional or inactive enzymes. The clinical  
 importance is highly dependent upon the patient's clinical state,  
 coadministered drugs, therapeutic index, and the relative importance of  
 the defective pathway in the total process of drug elimination. In  
 addition, a number of drugs can also act as P450 enzyme inhibitors, which  
 have the potential of causing drug interactions. In patient management,  
 it is important to consider the fact that most antidepressants can also  
 act as enzyme inhibitors. A number of adverse reactions resulting from  
 coadministration of tricyclic antidepressants and **SSRIs** have  
 been described. Such drug interactions can be minimized or avoided by  
 following simple clinical logic.